

# Screening for and Chemoprevention of Prostate Cancer

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The Spring of 2009 has seen the publication of two landmark studies on screening for prostate cancer. Unfortunately, they have arrived at different conclusions, so that, instead of settling the debate, they have only served to fuel the controversy that already surrounds this issue. The European Randomised Study of Prostate Cancer Screening (ERSPCS) demonstrated a 20% reduction in mortality in the screened arm of their study (Schroder *et al* NEJM 2009, 360:1320-8), while, by contrast, the US based PLC screening study reported no difference between the two arms at 9 years (Andriole *et al* NEJM 2009 360:1310-9). However, there are several important differences between the two studies that may account for the discrepancy. The European Randomised Study of Prostate Cancer Screening (ERSPCS) of 182,000 men was based on a cut-point of 3.0ng/ml rather than the 4.0ng/ml value selected for the US-based PLC screening study as a trigger for further investigations. This may have allowed the Europeans to identify more cancers at a stage when they were still curable. Another problem with the US-based PLC study of 76,693 men is the pre-existent widespread use of PSA screening within the population. This has led to the contamination of the non-screened arm by men who went and had their PSA tested outside the study. Clearly this will have significantly reduced the power of the trial to detect a difference between the two arms, especially since the US study recruited less than half the number of patients than the European group. Thus the jury remains out on this issue, but urologists and oncologists whose aim it is to reduce the death toll from prostate cancer will be encouraged that in the UK alone on the basis of the ERSPCS data 2000 lives per annum potentially could be saved; and with longer follow-up there is certainly the potential for an even greater reduction in mortality in the men screened for prostate cancer, but also a concomitant risk of over-diagnosis.

Over-diagnosis becomes less of an issue if a policy of active surveillance rather than immediate treatment is followed for those presenting with "low risk" prostate cancer. Moreover, there is now emerging data to confirm that chemoprevention of prostate cancer is possible. Three large-scale chemoprevention trials including SELECT (testing selenium and vitamin E), the Prostate Cancer Prevention Trial (PCPT) – testing the 5 alpha-reductase inhibitor finasteride, and REDUCE (testing dutasteride) are completed or nearing completion. The initial results of SELECT have now been

reported and find no benefit from either selenium or vitamin E on risk of prostate cancer (Lippmann *et al* JAMA 2008 147:217-23). The results of the REDUCE trial investigating dutasteride as a chemopreventative agent should be available shortly. The results of the PCPT demonstrated a significant (measured relative risk reduction of 24.8%) reduction of risk of prostate cancer (Thompson *et al* NEJM 2003; 349:215-24). The initial observation of an excess risk of high grade disease appears to be related to improved detection of cancer and high grade cancer related to improved sensitivity of PSA, digital rectal examination, and prostate biopsy for cancer and high grade cancer detection. Modelling studies suggest that with finasteride the risk of high grade cancer is either unchanged or reduced. Sexual dysfunction and gynaecomastia were observed but the rates were low and probably would not in themselves militate against the widespread use of a 5 alpha-reductase inhibitor to prevent prostate cancer.

In conclusion, the evidence-base for both screening for and chemoprevention of prostate cancer has increased recently, but many controversies remain. Certainly the data from Europe, where PSA testing is currently relatively uncommon, suggest that many lives could be saved by screening and chemoprevention strategies.